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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,827	12/14/2005	Marguerite A. Cervin	GC779-2-US	4369

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,827	CERVIN ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *1-32 and 38-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Action on the Merits of US Application No. 10/527,827, filed 14 December 2005, which claims priority to PCT/US03/31445, filed 3 October 2003, which claims priority to US Provisional Applications 60/416,167 and 60/416,192, both filed 4 October 2002. Claims 1-42 are pending. Claims 1-32 and 38-42 are withdrawn. Claims 33-37 are under examination in this action.

Election/Restrictions

Applicant's election with traverse of Group III (claims 33-37) in the reply filed on 18 December 2007 is acknowledged. The traversal is on the ground(s) that Applicants believe that a search of the entire application (or Groups 1 and 2) can be made without a serious burden. In addition, Applicants contend that there would not be a serious burden for examination between Groups 1 and 2, stating that Group 1 relates to a method of enhancing the production of a desired product in a bacterial host cell by inactivating an endogenous arcA gene and culturing in media containing glucose under aerobic condition, while group 2 relates to bacterial host cell containing an inactivated arcA gene. In addition, Applicants argue that these two groups are related as product and process claims. Furthermore, Applicants argue that the reference identified and cited in the previous office action does not teach an *E.coli* host cell with an inactivated endogenous arcA gene, and that it only discloses a mutant that is defective in regulating it's catabolic activity.

This is not found persuasive for reasons already of record and because, for example, the independent Claim 1 does not recite the claim limitation "an E.coli host

cell" and therefore, the Nystrom et al reference does anticipate the special technical feature which is therefore not novel. In addition, the invention of Group III does not require the special technical feature of an inactivated endogenous arcA gene. Therefore, the entirety of the claims do not relate to a single general inventive concept.

In addition, the different inventions of Groups I-III would impose a serious search burden for reasons already of record and, for example, because the inventions require searching different electronic resources and employing different search queries and prior art applicable to one invention would not likely be applicable to another invention and the different inventions are likely to raise different non-prior art issues under 35 USC 112, first paragraph.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-32 and 38-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 December 2007.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 is indefinite because Claim 37 recites the term "said bacterial strain" and it is unclear which of the two distinct bacterial strains referred to in Claim 36 (from which Claim 37 depends) provides the antecedent basis for "said bacterial strain" of Claim 37 because Claim 36 recites "said bacterial strain" (spanning lines 1-2) and "a bacterial strain" (line 2). Therefore, one of ordinary skill in the art would not be able to determine the metes and bounds of Applicants invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Culham et al in "The osmotic stress response and virulence in pyelonephritis isolates of *Escherichia coli*: contributions of RpoS, ProP, ProU and other systems" (Microbiology, June 2001, Vol. 147, 1657-1670, whole article).

Claims 33/34 are directed to genetically engineered bacterial strains comprising an inactivated/deleted endogenous rpoS gene.

Culham et al teach genetically engineered bacterial strains which comprise inactivated variants of an endogenous RpoS gene and deletion mutants of an endogenous RpoS gene and which are derivatives of *E.coli* K12 (for example, see abstract and page 1659).

Therefore, Culham et al anticipate all the limitations of Claims 33-34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Culham *et al*. (June 2001) as applied to claims 33-34 above, and further in view of Golovlev and Golovleva in "Physiology of Microbial Cells and Metabolic Engineering" (Microbiology, 2000, Vol. 69, pages 119-128, whole article) and further in light of Chou et al (1996) in "Genetic Manipulation of Stationary-Phase Genes to Enhance Recombinant Protein Production in Escherichia coli" (Biotechnology and Bioengineering, Vol., 50, pp. 636-642, whole article).

Claims 35-37 are directed to the bacterial strains of claims 33-34 (described above), and are taught by Culham *et al*. for the reasons above. Additionally, Claim 35 is drawn to the genetically engineered bacterial strain of claim 33 further comprising an over-expressed polypeptide having PEP carboxylase activity. In addition, Claims 36/37 are drawn to the genetically engineered bacterial strain of claim 33, wherein said

bacterial strain/*E.coli* has a PTS^-/Glu^+ phenotype, which was derived from a bacterial strain originally capable of utilizing a PTS for carbohydrate transport.

Culham *et al*. differs from the invention claimed in the instant claims 35-37 in that while it teaches genetically engineered bacterial strains which comprise inactivated variants of an endogenous RpoS gene and deletion mutants of an endogenous RpoS gene and which are derivatives of *E.coli* K12 (for example, see abstract and page 1659), Culham *et al*. fails to explicitly teach the strain further comprising the PTS-/glucose+ phenotype and over-expression of a polypeptide having PEP carboxylase activity.

Golovlev and Golovleva teach *E.coli* strains comprising the PTS-/glucose+ phenotype and over-expression of a polypeptide having PEP carboxylase activity in *E.coli* strains. For example, Golovlev and Golovleva teach an *E. coli* strain "in which the PTS of glucose transport has been replaced by the independent PTS of galactose and proton symport capable of nonspecific glucose transfer (page 124, right column, paragraph4, lines 12-16). In addition, Golovlev and Golovleva teach *E. coli* strains comprising the over-expression of a polypeptide having PEP carboxylase activity. For example, Golovlev and Golovleva cite the genetically engineered E. coli strain with an amplified PEP carboxylase gene (page 122, right column, ¶ 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the RpoS mutant strain constructs of Culham et al in the strain taught in Golovlev and Golovleva because Culham et al teach that the RpoS variants and deletion mutants were successfully used, were available, and that

the procedure for making the variants was routine (e.g. p.1659, ¶ 4-7). In addition, Golovlev and Golovleva teach that rpoS *E. coli* mutants provide "considerable increase in the production of recombinant proteins" in *E. coli* (page 124, ¶ 1).

One would have been motivated at the time the invention was made to have utilized the RpoS variants/deletions of Culham et al in the strains of Golovlev and Golovleva especially in light of Chou et al because Chou et al teach that the strain of *E.coli* mutated in the rpoS gene (also called the katF gene, p. 637, ¶ 3) was beneficial for recombinant protein production (e.g. page 639, left column). For example, Chou et al show an enhancement in the katF (RpoS) mutant strain for both systems tested in their study. In addition, Chou et al recite "the potential of using such genetic manipulations as an alternative strategy for bioprocess improvement was demonstrated to be attractive and fruitful" (page 640, right column). In addition, regarding the combination of the various metabolically relevant strains and rpoS regulatory system mutations, Golovlev and Golovleva recite:

> There are two possible approaches for elucidating regulatory influences on a rate-limiting step. The first approach is implemented in so-called inverse genetic
>
> engineering [97]. In terms of this approach, a rate-limiting step is somewhat modified by genetic engineering, and then the metabolic and regulatory consequences of this modification are thoroughly analyzed to form a basis for the next genetic engineering operation. The desired result (a more efficient recombinant strain) is achieved via a series of successive metabolic modifications. The second approach involves the numerical simulation of a metabolic block with allowance made for its multiple regulation [98]. It is obvious that a combination of these approaches may appear especially fruitful" (page 125 ¶ 3).

In addition, both Culham *et al*. and Chou *et al*. and Golovlev and Golovleva are in the same field of endeavor (bacterial metabolic engineering) and both are directed to the same problem sought to be solved (analysis of bacterial metabolic fluxes).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of *E. coli* RpoS mutants, the over-expression of PEP carboxylase, and the use of PTS-/glucose+ strains for the purpose of improving the efficiency of *E. coli* metabolic transport pathways was routinely practiced at the time of Applicants invention.

In view of the foregoing, the method of claims 33-37, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a).*

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert, Ph.D., whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert
Examiner/AU1636

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636